





for the Study of Pleura and Peritoneum

NOVEL THERAPEUTIC AGENTS FOR PLEURA & PERITONEAL CANCERS

CAR T-Cell Therapy for Pleural and Peritoneal Cancers

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Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura



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- > Licensing and Royalty: Mesothelin CAR and PD1 DNR licensed to Atara Biotherapeutics
- Patents (issued and applications): Mesothelin CAR, PD1DNR, CARs with new targets and costimulatory domain, Ex-vivo pleural effusion culture system (ePECS), Wireless pulse oximetry (Wipox) device, Detection of cancer cells by oncolytic virus

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.





Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed <u>Assembly Bill (AB) 1195</u>, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed <u>AB 241</u>, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

• Tobacco smoking related cancers and its influence on patient care.





Chimeric antigen receptor (CAR) T-cell therapy



- > CAR-T cell therapy is 56% of currently active cell therapies
 - > 299 new CAR-T cell agents from 2020-2021





CAR T-cell therapy successes in hematological malignancies (80% CR in ALL)

FDA approved therapy:

CD19-targeted CAR T cells (B-cell acute lymphoblastic leukemia, Non-Hodgkin lymphoma, Follicular lymphoma, Mantle cell lymphoma)

BCMA-targeted CAR T cells (Multiple myeloma)

CAR T-cell therapy for solid tumors



Science Sept 2016

Kiesgen S., Adusumilli PS. J Thorac Oncol 2017

Thoracic cancers CAR T-cell therapy: Mesothelin as an antigen target



Mesothelin-targeted CAR T-cell therapy: Preclinical



Adusumilli PS., Sadelain M. *Sci Transl Med* 2014 Cherkassky L, Morello A, Adusumilli PS. *J Clin Inv* 2016

Mesothelin-targeted CAR T-cell therapy: phase I clinical trial (NCT02414269, regional delivery in patients with pleural cancer: mesothelioma, lung and breast cancers)



Ghosn M., Adusumilli PS., Solomon SB. Lung Cancer 2022

Adusumilli PS., Sadelain M. Cancer Discovery 2021

Mesothelin-targeted CAR T-cell therapy: phase I/II clinical trial



Unpublished data

Please do not post

Ann Oncology 2022 May

Combination immunotherapy for solid tumors

Transforming cold solid tumors to hot and keep them warm

Cancer Cell Review

Combination Immunotherapy with CAR T Cells and Checkpoint Blockade for the Treatment of Solid Tumors

Rachel Grosser,¹ Leonid Cherkassky,² Navin Chintala,¹ and Prasad S. Adusumilli^{1,3,*}



Activation

Activated CAR T cells

yse tumor cells and

Exhausted CAR T cells

upregulate PD-1

Tumor cells upregulate PD-L1

CPB Intervention
T-cell based
PD1 DNR
PD1 CRISPR
PD1 scFv

Grosser R, Adusumilli PS. Cancer Cell 2019

ARTICLES

https://doi.org/10.1038/s41590-021-00975-5

Exhausted T cells are scarred

Aug 2021

Epigenetic scarring of exhausted T cells hinders memory differentiation upon eliminating chronic antigenic stimulation

Mohamed S. Abdel-Hakeem^{1,2,3}, Sasikanth Manne^{1,2}, Jean-Christophe Beltra^{1,2,4}, Erietta Stelekati^{1,2,8}, Zeyu Chen^{1,2}, Kito Nzingha^{1,2}, Mohammed-Alkhatim Ali^{1,2}, John L. Johnson^{2,5}, Josephine R. Giles^{1,2,4}, Divij Mathew^{1,2}, Allison R. Greenplate^{1,2}, Golnaz Vahedi^{2,6,7} and E. John Wherry^{(3),2,4}

ARTICLES nature immunology

Differentiation of exhausted CD8⁺ T cells after termination of chronic antigen stimulation stops short of achieving functional T cell memory

Pierre Tonnerre ¹²^{SC}, David Wolski¹, Sonu Subudhi^O¹, Jihad Aljabban¹, Ruben C. Hoogeveen¹, Marcos Damasio¹, Hannah K. Drescher¹, Lea M. Bartsch¹, Damien C. Tully^{O³}, Debattama R. Sen^{O4,5}, David J. Bean^{O³}, Joelle Brown^{O¹}, Almudena Torres-Cornejo¹, Maxwell Robidoux¹, Daniel Kvistad¹, Nadia Alatrakchi¹, Ang CuiO^{6,2}, David Lieb^{O⁶}, James A. Cheney¹, Jenna Gustafson¹, Lia L. Lewis-Ximenez⁸, Lucile Massenet-Regad^{O²}, Thomas Eisenhaure^{6,6}, Jasneet Aneja^{1,9}, W. Nicholas Haining^{O4,5}, Raymond T. Chung¹, Nir Hacohen^{O4,10}, Todd M. Allen^{O3}, Arthur Y. Kim⁹ and Georg M. Lauer^{O1SC}



nature

immunology

Epigenetic scars of CD8⁺ T cell exhaustion persist after cure of chronic infection in humans

Kathleen B. Yates [©]^{1,2,3}, Pierre Tonnerre [©]^{4,5}, Genevieve E. Martin [©]^{6,7}, Ulrike Gerdemann¹, Rose Al Abosy [©]¹, Dawn E. Comstock [©]^{1,8}, Sarah A. Weiss [©]^{1,8}, David Wolski⁴, Damien C. Tully [©]^{9,10}, Raymond T. Chung⁴, Todd M. Allen [©]⁹, Arthur Y. Kim¹¹, Sarah Fidler^{12,13}, Julie Fox^{14,15}, John Frater [©]^{6,16}, Georg M. Lauer [©]⁴, W. Nicholas Haining [©]^{11,718} [⊆] and Debattama R. Sen [©]^{12,18} [⊆]



Mesothelin-targeted CAR T-cell therapy with T-cell intrinsic check point blockade (M28z1XXPD1DNR, NCT04577326)

A decoy receptor may prevent exhaustion PD1DNR: A decoy receptor CAR

M28z1XXPD1DNR Tumor Treadmill Test demonstrates functional persistence

(2 months after pleural tumor eradication, mice were challenged with increasing doses of tumor cells)





Adusumilli PS. ESMO 2021

Hurdles in solid tumor cell therapy



Kiesgen S., Adusumilli PS. J Thorac Oncol 2017

Adusumilli PS., Sadelain M. Cancer Discovery 2021

Targeted tumor antigen heterogeneity limits CAR T-cell efficacy



Targeting high-antigen expressing cancer cells while sparing lowantigen expressing normal cells in necessary to avoid on-target, offtumor toxicity

In vivo survival

100-

50-

N=30 p<0.05



New co-stimulatory domain to promote cytotoxicity against low-antigen expressing tumor cells in IND studies

Control T cells Antigen low 50 100 Kiesgen S., Adusumilli PS. J Thorac Oncol 2017 Days after tumor injection Zeltsman M., Adusumilli PS. Transl Res 2017 Kachala S., Adusumilli PS. Clin Cancer Res 2014

CAR T cells

Antigen high

High content screening of 2688 FDA approved oncological agents using a high-throughput confocal imaging platform



Unpublished data

An ex vivo pleural effusion culture system (ePECS)



Influence of MPE on CAR T-cell efficacy

Co-culturing patient's T cells transduced with next-gen CARs in pleural effusion provides insights into inhibitory factors

Unpublished data



Regional delivery of CAR T cells

Regional CAR T-cell therapy: an ignition key for systemic immunity in solid tumors



Swarming effect

Regional delivery of CAR T cells

Antigen-activated CAR T cells alter tumor immune microenvironment

Promotes tumor-infiltration of systemically delivered CAR T cells

Unpublished data

DoD funded trial to be initiated:

Intraperitoneal delivery of CAR T cells in patients with peritoneal carcinomatosis

Cherkassky L., Adusumilli PS, Cancer Cell 2022

CAR T-cell therapy for solid tumors Mesothelin-targeted CAR T-cell therapy Translational path: clinical sample analysis to mouse models to trials



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CAR T-Cell Therapy for Pleural and Peritoneal Cancers

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